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# **Functional and structural MRI correlates of fatigue in patients with Rheumatoid Arthritis**

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## **Abstract**

**Objectives:** Fatigue is a major burden among patients with rheumatoid arthritis (RA) yet is poorly understood. We sought to conduct the first imaging study to investigate the neurobiological correlates of fatigue in RA and to improve upon the methodological limitations of previous neuroimaging studies which have investigated this symptom in other populations.

**Methods:** Chronically fatigued RA patients were clinically characterised before undertaking a combined functional and structural mode MRI brain scan. The functional sequences were acquired during a fatigue evoking task then network to whole brain analyses were undertaken. The structural analyses employed voxel based morphometry in order to quantify regional grey matter volume. The scan was repeated 6 months later to test reproducibility.

**Results:** Fifty-four participants attended both scans (n=41 female; baseline mean (SD) age and  $54.94 \pm 11.41$  years). A number of significant functional and structural neural imaging correlates of fatigue were identified. Notably, patients who reported higher levels of fatigue demonstrated higher levels of functional connectivity between the Dorsal Attention Network and medial prefrontal gyri – a finding which was reproduced in the repeat scans. Structurally, greater putamen grey matter volumes significantly correlated with greater levels of fatigue).

**Conclusions:** Fatigue in RA is associated with functional and structural MRI changes in the brain. The newly identified and reproduced neural imaging correlates provide a basis for future targeting and stratification of this key patient priority.

**Key words:** fatigue; rheumatoid arthritis; neural imaging correlates; functional connectivity; voxel based morphometry

## **Key Messages**

1. Fatigue in rheumatoid arthritis is associated with functional and structural brain changes
2. The neural processes of rheumatoid arthritis fatigue may overlap with those related to pain and depression

## **Introduction**

Fatigue is a symptom which is common to many chronic diseases<sup>1</sup> and is especially prevalent and burdensome among musculoskeletal disorders such as rheumatoid arthritis (RA)<sup>2-5</sup>. As many as 80% of RA patients report significant levels of fatigue and over 70% consider fatigue to be equal to pain in terms of burden<sup>6</sup>. Yet patients feel this symptom is disregarded and physicians are frustrated by insufficient therapeutic options - a situation that is ultimately attributable to our limited mechanistic knowledge of this complex symptom.

Epidemiological investigations of RA related fatigue support a multi-factorial origin. In particular, strong associations with central factors such as mental health have been commonly reported<sup>6 7</sup>. These observations reinforce evidence from other significantly fatigued populations where advanced magnetic resonance imaging (MRI) of the central nervous system (CNS) has been the only experimental methodology to consistently identify fatigue-related abnormalities<sup>8</sup>.

MRI methods tested to date include voxel-based morphometry (VBM). This has frequently evidenced fatigue-associated structural alterations in grey matter volumes<sup>9 10</sup>. Such changes are likely to evolve over time, although some studies suggest this may occur in as short as a

week following a neuro-modulatory intervention <sup>11</sup>. By contrast, functional MRI (fMRI) studies essentially provide a surrogate measure of neuronal activity<sup>12</sup>. As with other complex symptoms (e.g. depression), task-based fMRI paradigms of fatigue have implicated numerous diffuse neural correlates indicating that such higher order processes are not limited to single regions. Recent functional connectivity analyses of MRI data (fcMRI) – which assay interconnected regions of the brain - has evidenced significant abnormalities related to fatigue in the connections between established brain networks in the context of multiple sclerosis <sup>13 14</sup> and Parkinson's disease <sup>15</sup>.

Despite the accumulating evidence implicating the brain with fatigue, no consistent regions or patterns have been reported. There may be multiple methodological reasons to explain this situation. First, variations in analytical approach are common and no studies have attempted to validate their results by employing the same design and techniques. Second, almost all existing studies are comprised of small sample sizes ( $n < 30$ ) which are notorious for generating unreliable results in neuroimaging <sup>16</sup>.

Here we report the first MRI brain study to specifically investigate the neural correlates of fatigue in a RA population. We aimed to improve upon the methodological limitations of previous non-RA fatigue neuroimaging studies by recruiting a large sample size and incorporating a reproduction phase. We also explored the relationship between fatigue specific neural imaging correlates and other clinical factors which are implicated with fatigue on an epidemiological level in order to understand whether these associations also exist on a neurobiological level.

## Methods

*Design:* Observational cohort study

*Sample:* RA patients attending a UK regional rheumatology service were consecutively approached. Those who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria <sup>17</sup> and who experienced fatigue for >3 months at clinically significant levels (Chalder fatigue binary scale >3 <sup>18</sup>) were considered eligible. Patients with contra-indications to MRI (e.g. pacemaker in situ), alternative medical explanations for fatigue or left handedness, were excluded.

Full written informed consent was obtained according to the Declaration of Helsinki and then these final participants were stratified (1:1) according to those with and without active RA, where active disease was defined as a swollen joint count>1.

We aimed to recruit >50 since this provides the power to detect moderate sized correlations at relatively conservative thresholds (i.e.,  $r = .46$  for  $\alpha = .001$ ) and are considered to perform well in the functional connectivity analytical approach that we have adopted <sup>19</sup>.

*Procedure:* All consenting participants underwent a phenotyping battery and multi-modal MRI brain scan (Achieva 3T X-series MR system, Philips Medical Systems). This procedure was repeated at a second session, 6 months later, for the purposes of reproduction.

*Phenotyping battery* (primary and secondary and clinical outcomes): The primary clinical outcomes of interest were fatigue assessed by the Bristol Rheumatoid Arthritis Fatigue (BRAf) numerical rating scale (NRS) for severity, employing both current and 1 week periods of recall. Subjects report a score of 0-10 with anchors of “No fatigue” to “Totally exhausted. Higher

scores reflect greater problems for severity. The BRAF enjoys high acceptability, test-retest reliability and content, construct and criterion reliability<sup>20</sup>.

Secondary clinical outcomes were selected based on previous epidemiological studies evidencing their role as putative determinants of RA related fatigue: systemic inflammation<sup>21</sup>, C reactive protein (CRP); pain, current levels of pain severity<sup>6</sup>, 0-10 NRS; sleep disturbance<sup>22</sup>, as measured by the Jenkin's sleep scale<sup>23</sup>; depression<sup>6</sup>, Hospital Anxiety and Depression Scale<sup>24</sup> and fibromyalgia (FM)<sup>25</sup>, 2011 Fibromyalgia survey score<sup>26</sup>.

*MRI brain measures:* Images were acquired by a 3 Tesla, 8 channel phased array head coil using 3D T1 and T2\*-weighted gradient-echo echo-planar imaging pulse sequences. Since previous studies of non-RA populations have failed to report common findings, we adopted a data driven whole brain search for regions connected to plausible fatigue related networks.

#### Functional connectivity MRI (fcMRI):

*Acquisition and pre-processing:* see appendix for parameters. The functional sequences were obtained using a block design where a cognitive task (the paced auditory serial additional test, PASAT) was undertaken during 3x3 minute 'on' periods and interspersed by 4x30 seconds rest or 'off' periods. The PASAT has been successfully employed in fMRI paradigms to evoke fatigue both in its original and modified forms<sup>27-30</sup>, although its capacity to specifically induce clinically relevant RA fatigue has yet to be validated. In this study, subjects listened to a series of randomly generated numbers, between 1 to 9 and were asked to add consecutive numbers (i.e. the first and the second, the second and the third, etc.). When two consecutive numbers totalled 10, they were asked to press a button. Concurrently they were requested to focus on a computer screen displaying three boxes containing randomly changing numbers (between 1-10). They were instructed not to process the visual numbers whose role is primarily distract

the subjects from the auditory task with a view to increasing its complexity and subsequent fatigue.

*Independent Component Analysis (ICA):* Group ICA was performed using the fMRI Toolbox (GIFT) toolbox <sup>31</sup>, see appendix for parameters. Only components previously implicated with fatigue were analysed: a) default mode network (DMN) has been associated with cancer related fatigue <sup>32</sup> b) dorsal attention network (DAN) with fatigue in AS <sup>10</sup> c) salience network (SLN) with chronic fatigue syndrome <sup>33</sup> d) sensorimotor network (SMN) with Parkinson's disease and multiple sclerosis related fatigue <sup>14 15</sup>.

*Functional connectivity analysis:* Seed to whole brain connectivity was performed using the CONN (Cognitive and affective neuroscience laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA; [www.nitrc.org/projects/conn](http://www.nitrc.org/projects/conn)) functional connectivity toolbox v15 in SPM8 <sup>34</sup>. White matter, CSF, and motion parameters were entered into the analysis as covariates of no interest. A band pass filter (frequency window: 0.01–0.1 Hz) was applied to remove linear drifts and high frequency noise from the data. The seeds used were based on the spatial masks of the intrinsic networks generated from the ICA analyses. The onsets of the task periods were included in the analysis, to measure connectivity between the network and the rest of the brain during each condition of the scanning period. First-level analysis included bivariate correlations between voxels within each network and all voxels throughout the whole brain, thereby creating separate beta maps for each individual at each session. Because we were interested in the task period, beta maps that measured network connectivity during the PASAT task were then passed onto group second-level analyses in SPM8. Here associations in intrinsic network connectivity and current (since this recall period better reflects the real-time nature of fMRI) fatigue NRS during the first session were



assessed using a General Linear Model, correcting for age and sex. The resulting maps were thresholded at a whole brain  $p < 0.001$  uncorrected voxel threshold and  $p < 0.05$  false discovery rate (FDR) cluster corrected for multiple comparisons. Significant regions were extracted from first-level network-to-whole brain connectivity maps for each subject by obtaining the average fisher transformed  $r$  values of the identified clusters. We then performed univariate correlation analyses for all remaining secondary outcomes of interest, followed by multivariate regression analyses to establish the independence of any observed associations. Finally, reproduction of these significant clusters were tested with a region of interest analysis by extracting the average fisher transformed  $r$  values of the 5mm spheres - created around the significant peak cluster coordinates using the Marsbar toolbox <sup>35</sup> - from the relevant second session network connectivity maps obtained 6 months later and then correlating with concurrent fatigue values. These post-hoc analyses were conducted in STATA 12.1 (Stata, College Station, TX, USA), statistical significance was set at a  $p$ -value of 0.05 two-sided.

#### Voxel based morphometry (VBM):

*Acquisition:* Inspection of each T-1 weighted fast-field echo data set that was used for normalization revealed no gross anatomical abnormalities.

*Pre-processing:* The images were then preprocessed using SPM8 using the Diffeomorphic Anatomical Registration using the Exponential Lie Algebra (DARTEL) toolbox <sup>36</sup>, see appendix for approach.

*Statistical analysis:* Simple descriptive statistics were used to report patient characteristics. Smoothed GM images were entered into a multiple regression analysis in SPM8 with NRS fatigue as the covariate of interest, with a 1 week recall period which is more relevant to MRI

metrics such as VBM which take time to change. . All analyses were controlled for total intracranial volume (the sum of GM, WM and CSF), age and sex. An absolute threshold mask of 0.1 was applied to exclude edge effects and non-homogenous voxels. Results were derived from a whole brain uncorrected voxel threshold of  $p < 0.001$  and deemed significant at  $p < 0.05$  FDR corrected for multiple comparisons. Significant regions were extracted from the normalized, smoothed GM images for each subject resulting in raw GM values that were imported into STATA 12.1 for post-hoc correlations with other clinical symptoms. Again, we were interested in validating the observed structural changes from session 1 at the repeat session 6 months later. As similarly described above, the ROIs were defined as the 5mm spheres created around the significant peak cluster co-ordinates from the session 1 whole brain analyses. We extracted participant specific raw GM volumes for all of the voxels within each ROI in session 2, and then performed regression analyses to examine the relationship with the primary clinical outcomes in STATA 12.1 (total intracranial volume, age, sex corrected). Statistical significance was set at a  $p$ -value of 0.05 two-sided.

## Results

*Patient characteristics:* Of the 335 patients approached, 54 met eligibility criteria and attended both MRI sessions (mean (SD) age  $54.94 \pm 11.41$  years;  $n=41$  female; mean (SD) disease duration  $11.49 \pm 8.64$  years). Levels of fatigue and other clinical characteristics were comparable between visits (table 1). The PASAT significantly ( $p<0.001$ ) increased fatigue during both visits (visit 1: mean increase 2.35 SD 1.75; visit 2: mean increase 1.44 SD 2.23)

[Table 1 insert]

*Functional brain network to region connections relate significantly to levels of fatigue*

Network to whole brain analysis of the baseline visit identified a number of significant connections which related to current levels of fatigue (figure 1). All *a priori* selected networks, except for SLN, were associated with at least one region (table 2). There was a significant correlation between SMN connectivity to the L insula and current NRS fatigue ( $r=0.48$ ,  $p=0.012$ , FDR corrected). Similar positive correlations were recorded for DMN-R middle frontal gyrus ( $r=0.59$ ,  $p=0.017$ , FDR corrected), DAN-L medial prefrontal cortex ( $r=0.50$ ,  $p=0.043$ , FDR corrected) and DAN-R medial prefrontal cortex ( $r=0.56$ ,  $p<0.001$ , FDR corrected) functional connections.

Region of interest analysis of session 2 data reproduced the significant associations between DAN to L and R medial frontal connectivity and current fatigue (figure 2 and table 3).

[Table 2, 3 insert]

*Regional grey matter volumes are significantly associated with fatigue*

Patients with greater grey matter putamen volumes reported higher average 1 week levels of fatigue (right:  $r=0.31$ ,  $p=0.03$ , corrected for total intracranial volume, age, sex and FDR) (figure 3 and supplementary table 1). However, The R putamen grey matter volume was not significant at session 2 ( $r = 0.20$ ,  $p=0.17$ ). L putamen grey matter volume was significantly associated with fatigue (1 week average) 6 months later ( $r= 0.30$ ,  $p=0.03$ , corrected for total intracranial volume, age and sex).

*Neural imaging correlates of fatigue are associated with other clinical features*

Some brain regions demonstrating functional connections with *a priori* networks relating to current fatigue, were also significantly (albeit less strongly) correlated with other clinical features previously implicated with fatigue in RA (supplementary table 2). The SMN-L insula connection correlated with pain, both current and chronic widespread aspects, – as captured by the ACR FM scale. The DMN-R middle frontal and DAN-R medial prefrontal connections both related to FM and depression, while the DAN-L medial prefrontal was also associated with depression in addition to current levels of pain. Neither inflammation nor sleep disturbance appeared relevant to any of these specific functional connections. Multivariate analysis, adjusting for all outcomes of interest, identified current fatigue as the principal independent association for each of these functional connections (supplementary tables 3-6).

Depression was significantly associated with greater putamen grey matter volume ( $r=0.35$ ,  $p=0.01$  and  $r=0.40$ ,  $p=0.003$ , R and L respectively). No other clinical associations with putamen grey matter volume were noted (CRP, pain, sleep disturbance, FM all  $p>0.05$ ).

## **Discussion**

This is the first study to examine the role of the CNS in fatigue among RA patients. Moreover, to the best of our knowledge, it is the largest multi-modal MRI brain investigation of co-morbid fatigue to have been conducted in any disease and the only study to test reproducibility. We have identified a number of functional and structural neural imaging correlates of RA related fatigue. In particular, patients who reported higher levels of fatigue

demonstrated higher levels of functional connectivity between the DAN and bilateral medial prefrontal gyri – a finding which was reproduced on repeat scanning. Structurally, greater putamen grey matter volumes also seemed to correlate with greater levels of fatigue. Finally, while the identified neural regions most strongly and independently related to fatigue, many also associated with other clinical features such as pain and depression. This further evidences the multifactorial nature of this key symptom at a neurobiological level.

Large proportions of neuroimaging results (including all known fatigue studies) fail to be reproduced <sup>37</sup>. The reproduction of the association between fatigue and DAN-medial prefrontal functional hyperconnectivity in the second set of scans is therefore reassuring. Anatomically, the DAN constitutes the frontal eye fields (a region at the intersection of the middle frontal and pre-central gyri) and the posterior parietal sulcus, both structurally connected by the superior longitudinal fasciculus. A key role of this major functional network is the top-down guided control of attention in response to predictable stimuli <sup>38</sup> which complements the ventral attention network's bottom-up control of attention in response to unexpected stimuli. Interestingly, these networks interface within the medial prefrontal gyrus where they are known to dynamically interact with each other <sup>38</sup>. A previous functional connectivity study of fatigue related to mild traumatic brain injury (mTBI) implicated the medial prefrontal gyrus with significant fatigue. Subjects undertook a complex cognitive task and the authors speculated that subtle brain structural injuries in mTBI led to a disruption to the attentional functional networks involving the medial prefrontal gyrus. The subsequent extra effort required to maintain task performance may then result in up-regulation of functional connectivity in relation to the attention networks <sup>39</sup>. Furthermore, a structural MRI study of ankylosing spondylitis (AS) related fatigue found individual fatigue scores to be negatively correlated with grey matter volumes of the dorsal and ventral attention networks

as well as reductions in the white matter integrity of the superior longitudinal fasciculus <sup>10</sup>. Certainly the close association between attention and fatigue has been commonly reported in the psychology literature. Kaplan et al described the neuropsychological phenomenon 'directed attention fatigue' as a consequence of an imbalance in the brain's attention mechanisms <sup>40</sup>.

Not all functional connections were reproduced, although there was a trend towards significance for the SMN-Insula and we have previously related DMN-frontal connectivity in cancer related fatigue<sup>32</sup>.

The prominence of the putamen in relation to fatigue is also noticeable, although statistical significance and laterality was not consistent between time points and so this may be a spurious finding. It is, however, striking to note that an identical positive correlation was observed between the putamen grey matter volume and fatigue in the only other neuroimaging study of co-morbid fatigue in an inflammatory arthritis (AS) <sup>10</sup> thus implying that this may be a generic fatigue pathway. Certainly, without a general population control group we are unable to attribute the identified neural imaging correlates specifically to RA.

Biologically, the putamen mediates reward responses <sup>42</sup> and so inactivity may translate into low motivation levels: a key dimension of fatigue in RA <sup>5</sup>. We speculate that the greater putamen grey matter volumes observed among the more fatigued RA patients might represent a compensatory mechanism in response to low putamen activity.

It appears that many fatigue CNS pathways could also be relevant to other clinical features. This current study evidences shared neurobiological associations with a number of candidate factors. For example, depression can clinically overlap with fatigue in RA <sup>43</sup>. Neurobiologically, the medial prefrontal gyrus is a recognised neural hub of depression <sup>44</sup> and

so it is intriguing to observe its co-existing association with fatigue in this cohort. The current analyses, in light of the existing literature, biologically validates the multifactorial nature of RA related fatigue, and begins to delineate overlapping pathways and so potentially aiding the future stratification of patients towards the most appropriate mechanism informed treatments.

Unlike many previous neuroimaging investigations of fatigue, our study has been primarily designed to investigate this prevalent symptom. Moreover, we sought to learn from previous methodological weaknesses in fatigue neuroimaging research from other populations by recruiting a large sample and incorporating a reproduction phase. However, certain study limitations exist. Firstly, as previously mentioned, without control groups this study is unable to inform the specificity of the identified neural imaging correlates. Indeed, given the aforementioned similarities in the literature of other clinical conditions, it could be speculated that the neural correlates of fatigue are generic. Secondly, these analyses are cross-sectional and so the identified neural regions are not necessarily causal. Alternatively, they may reflect downstream markers. This, nonetheless, would still represent progress since currently no reproducible objective measures of fatigue currently exist. The multitude of subjective fatigue measures vary greatly in their reliability<sup>20</sup> and their development have never been informed by the physiological construct of interest. Thirdly, although functional connectivity is mainly considered a measure of intrinsic communication networks (i.e. sub-conscious brain activity)<sup>45</sup>, it is possible that the PASAT (a task design to test attentional capacity and known to enhance brain activation within the attention brain networks<sup>46</sup>) has unmasked the importance of the DAN. While this strengthens the neuropsychological rationale for the importance of attention in the context of fatigue, it does mean that future attempts to replicate this finding using non-task based 'resting state' paradigms may be unsuccessful.

Moreover, while we appear to have evidenced the fatiguing nature of the PASAT, we must recognise that the experience of the MRI scanner can be fatiguing in itself and so potentially contributory to our observations. Finally, this task is likely to evoke other dimensions of cognition and it is unknown whether the fatigue is clinically relevant or more akin to the normal phenomenon of tiredness.

In the future, applying machine learning methodologies to even larger sample sizes may help stratify fatigued patients according to a specific mechanistic pathway and subsequent triage towards a personalised treatment. For example, a patient with a neurobiological signature which overlaps between fatigue and depression may benefit from anti-depressants. In parallel, neuromodulation of the identified correlates offers one way to test the causality of the selected neural regions and, if found to alleviate fatigue, offers a potential therapy for primary fatigue. Whether these correlates are disease specific or generic is unknown. Further validation of neuroimaging studies in distinct fatigue populations are required. Finally, the highlighted role of the DAN, emphasises the potential importance of attention in RA related fatigue. Behavioural interventions, such as mindfulness, can be effective in enhancing attention<sup>47</sup> and so may also have a role in treating fatigue.

In summary, we report the first study to directly implicate the CNS in the pathophysiology of fatigue among RA patients. Higher levels of fatigue related significantly to a number of functional and structural changes in the brain. These neural imaging correlates were also relevant to other clinical features, mirroring the multifactorial nature of fatigue inferred from previous epidemiological studies. This data not only provides preliminary targets for much needed primary fatigue therapies, but also forms a basis for the future neurobiological stratification of patients. Fatigue is the most heterogeneous of constructs and so ultimately



clinicians require the tools to ensure individual patients receive the most mechanistically relevant treatments for their individual fatigue.

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NB, CK, EI, AS, TL, GW, AM, RH and DC were involved in designing the study and interpreting the data, drafting the article and revising it critically for important intellectual content. All authors approved the final version to be published. NB and CK analysed the data and NB and RH wrote the first draft. EI, TL and GW contributed to the data analysis. NB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

### **Conflicts of interest**

REH, NB, GW, AM, DC have received research funding from Pfizer. DC has received research funding from Aptinyx, Cepherex and personal fees from Abbott Pharmaceutical, Aptinyx, Cerephex, Pfizer, Daiichi Sankyo , Pierre Fabre, Samumed, Therevance, Tonix, Williams & Connolly LLP, Zynerba, Astella. CK, EI, TL, AS have no disclosures.

### **Ethical approval**

Ethical approval for the study was obtained from the North of Scotland Research Ethics Committee and all participants gave informed written consent according to the Declaration of Helsinki.

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## Tables

Table 1: Mean clinical characteristics

	Baseline visit	6 month visit
RA disease activity <sup>a</sup>	3.62±1.30	3.39±1.36
CRP (mg/L)	7.78±8.54	7.52±10.81
Fatigue (current) <sup>b</sup>	4.59±2.19	4.91±2.01
Fatigue (1 week average) <sup>c</sup>	6.19±1.82	5.52±1.99
Sleep disturbance <sup>d</sup>	15.67±5.46	14.46±5.60
Current Pain <sup>e</sup>	3.81±2.38	2.91±1.92
Depression <sup>f</sup>	6.89±3.92	6.13±3.80

<sup>a</sup>Disease activity score 28; <sup>b</sup>Current fatigue 0-10 numerical rating scale (NRS); <sup>c</sup>Average NRS of fatigue during the past 7 days; <sup>d</sup>Jenkin's sleep scale; <sup>e</sup>Current pain NRS; <sup>f</sup>Hospital Anxiety and Depression Scale

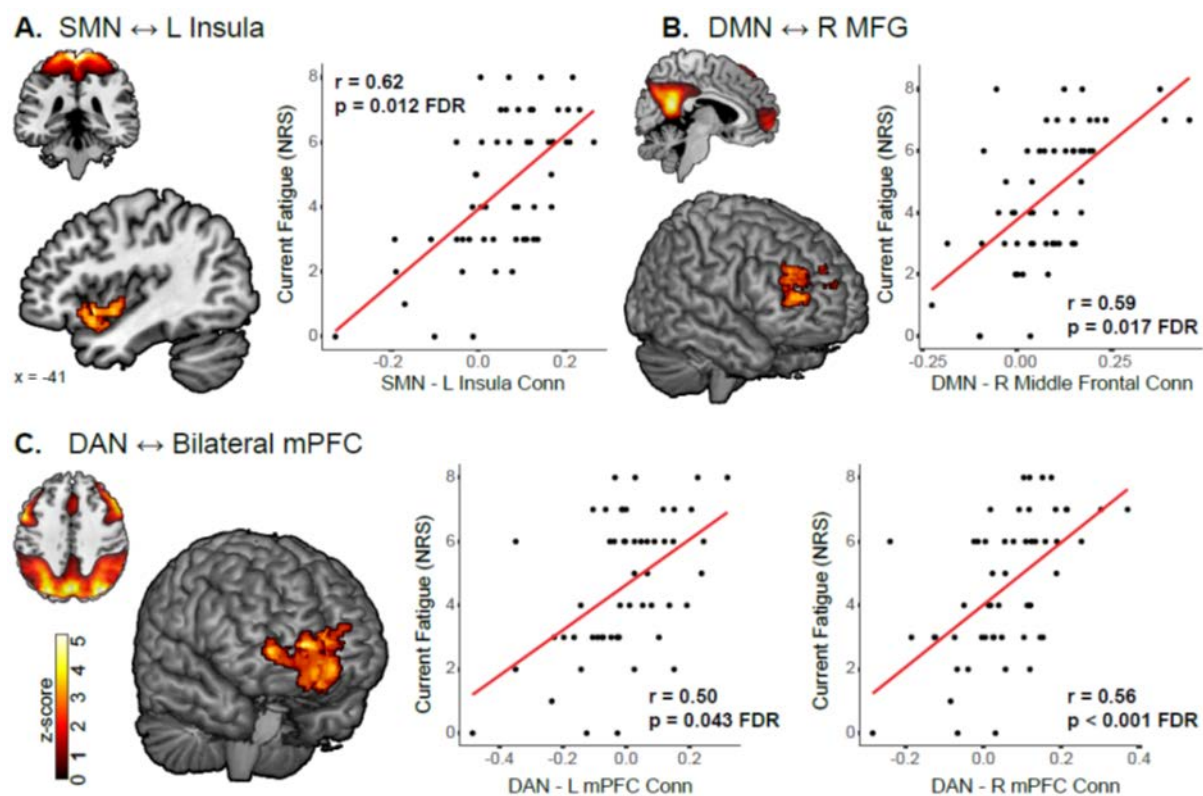
Table 2: Network to whole brain connectivity associations corrected for age and sex with current fatigue (session 1)

<b>Network</b> FC region (direction of association)	MNI co-ordinates (x, y, z)	Z score	Cluster size (voxels)	p value, FDR
<b>Sensorimotor (SMN)</b> L Insula (+ve)	-44, 14, -8	4.50	166	0.012
<b>Default mode (DMN)</b> R Middle Frontal (+ve)	42, 56, 26	4.27	169	0.017
<b>Dorsal attention (DAN)</b> L Medial Prefrontal (+ve)	-10,50,-12	3.70	102	0.043
R Medial Prefrontal (+ve)	8, 54, 0	4.59	300	<0.001

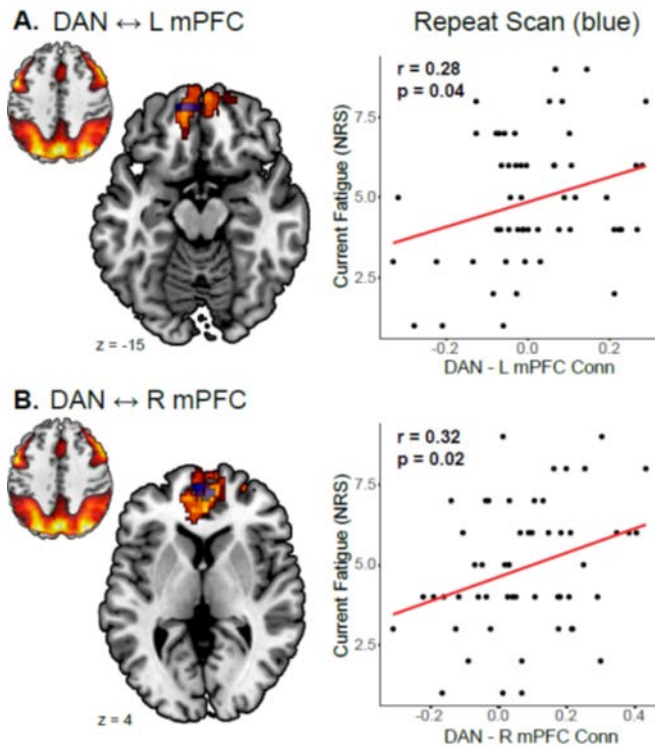
Table 3: Region of interest functional connectivity reproduction of current fatigue analysis (session 2)

<b>Network</b> FC region	Pearson correlation co-efficient	p value
<b>Sensorimotor (SMN)</b> L Insula	0.21	0.13
<b>Default mode network (DMN)</b> R Middle Frontal	0.09	0.52
<b>Dorsal attention network (DAN)</b> L Medial Prefrontal R Medial Prefrontal	0.28 0.32	<b>0.040</b> <b>0.020</b>

## Figures

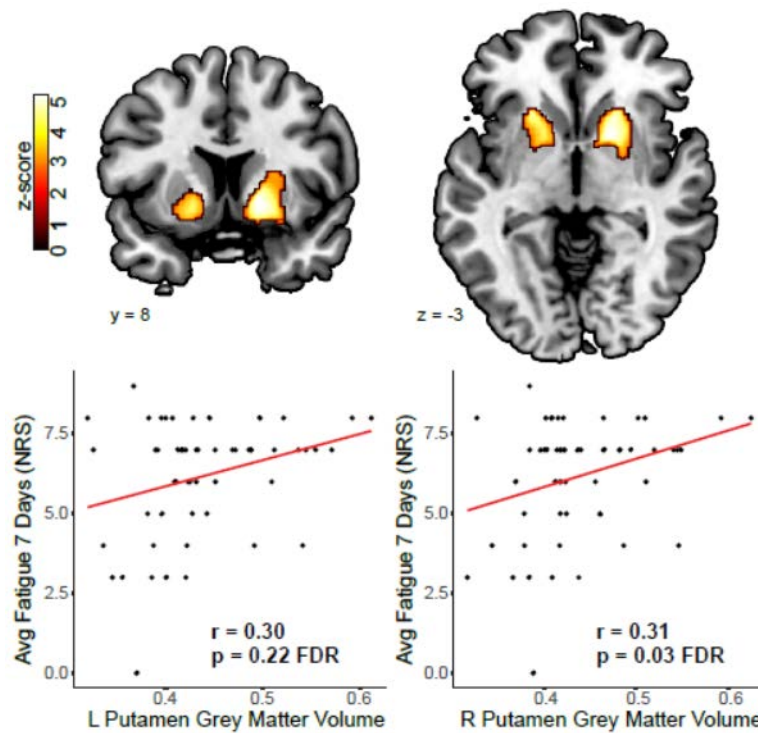


**Figure 1:** Increased brain connectivity between the SMN and Left Insula (A); DMN and Right Middle Frontal Gyrus (B); DAN and bilateral medial prefrontal cortex (C) is associated with current levels of fatigue in patients with rheumatoid arthritis. Scatter plots show positive correlations for interindividual differences in brain connectivity (Fisher transformed  $r$ -values; x-axis) and the current fatigue ratings (y-axis).



**Figure 2:** The association between DAN-bilateral prefrontal hyperconnectivity and current fatigue ratings was reproduced on repeat scanning. The significant session 2 cluster (BLUE) is superimposed on the significant session 1 cluster (ORANGE). Scatter plots show positive correlations for interindividual differences in brain connectivity (Fisher transformed  $r$ -values; x-axis) and current fatigue ratings (y-axis).





**Figure 3:** Patients with greater grey matter putamen volumes reported higher average 1 week levels of fatigue. Scatter plots show positive correlations for inter-individual differences in grey matter volumes (raw volumes; x-axis) and 1 week average fatigue (y-axis),<sup>b</sup>corrected for total intracranial volume, age, and sex. The R but not L putamen grey matter volumes were statistically significant.

NB: All brain illustrations are presented at  $p=0.005$  FDR threshold.